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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/381,344	09/20/99	SEEMANN G	2481.1640

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EXAMINER	
SHUKLA, R	
ART UNIT	**PAPER NUMBER**
1632	11

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/381,344	Applicant(s) SEEMANN ET AL.	
	Examiner Ram Shukla	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 August 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 4-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 4-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 9 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Response filed 4-02-01 and the supplemental response filed 8-10-01 have been entered.

2. Claims 2 and 3 have been cancelled.

3. Amendments to claims 1, 4, 9, and 10 have been entered.

Election/Restrictions

4. Applicants' election of p15-deoxyspergualin is acknowledged. Applicant's election with traverse of osteoarthritis with respect to claims 7, 14, and 15 in Paper No. 10 is acknowledged. The traversal is on the ground(s) that claims 7 is dependent on claim 1 which recites increasing tolerance to transplanted transgenic cells into a mammal and therefore regardless of a particular disease being treated tolerance to gene therapy would be improved. This is not found persuasive because the immune reaction due to a transplanted transgenic cell would depend on multiple factors, such as the transgene being expressed, vector being used for gene delivery, source, nature and characteristics of the cells being transplanted, etc. therefore, improvement in tolerance to gene therapy would not be regardless of a disease being treated. Antigens present both in the viral vector and the transgene product cause cellular and humoral immune responses dependent on the viral vector, the route of administration, and the genotype and infection history of the host (Hackett et al, Curr. Opin. Mol. Ther. 2:376-382, 2000, abstract). Accordingly, the immune tolerance due to an agent would depend on all these factors and would vary based on these factors.

The requirement is still deemed proper and is therefore made FINAL.

5. Claims 1 and 4-15 are pending.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1 and 4-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of increasing the tolerance of a mammal to transgenic cells, wherein the transgenic cells are produced in vivo after the administration of a vector carrying a transgene, by administering p15-deoxyspergualin to the mammal intravenously or intraperitoneally, before, during or after the administration of the vector, wherein said transgene encodes a protein, wherein a concomitant immunosuppressant therapy is discontinued, does not reasonably provide enablement for increasing tolerance in a mammal to transgenic cells produced in vitro or wherein the transgene of the transgenic cells produces a therapeutic protein that effects a treatment of a disease or wherein the transgenic cell produced in vivo after administration of a vector in vivo produce treatment of any disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the

existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

It is noted that the claimed invention is for increasing tolerance to transgenic cells in a mammal or a man, by administering p15-deoxyspergualin during, before, or after the administration of the transgenic cells, wherein the cells are produced in vitro or in vivo and wherein the method is for treating a disease by gene therapy and the disease is osteoarthritis, AIDS, hepatitis or diabetes and wherein the cells are transfected by a recombinant adenovirus vector or wherein the method is for vaccination. However, the specification is not enabling for the broad scope of the claimed invention because the specification as filed fails to teach as to how an artisan of skill would have administered or would have increased the tolerance of transgenic cells in a mammal including a man wherein the transgenic cells were from the same or different species expressed any gene or where the method was for treating any disease by gene therapy or by ex vivo cell therapy. An artisan of skill would have required undue experimentation to make and use the claimed invention commensurate with the scope of the claimed invention because the art of cell transplantation and immune tolerance was unpredictable at the time of the invention and the specification does not provide sufficient guidance as to how an artisan of skill would have addressed the unpredictability issues raised in the art.

The specification on pages 2-5 provides a general sketchy description of using immunosuppressants for increasing tolerance of transgenic cells in a mammal, and lists different immunosuppressants, different protein that are

therapeutic and different diseases. The specification also provides a general approach of treating a disease using gene therapy approach in in vivo or in vitro situations or by DNA vaccination. The specification also states that the pharmaceutical of the claimed invention could be administered by different routes. However, it is noted that the specification does not provide any guidance as to how a transgenic cells would be prepared in vitro or how a transgenic cell would be administered to a mammal or what doses of the cell would be used or as to how the pharmaceutical p15-deoxyspergualin would be administered to a mammal intranasaly, topically, percutaneously, topically, by inhalation or by other 15-16 routes of administration. It is noted that out of the listed routes of administration (claim 9), art only teaches administration of p15-deoxyspergualin (DSG) by intravenous infusion (see page 4 in reference # 16 of the IDS filed 5-31-01) or i.p. In other words, neither the prior art nor the specification teaches as to how an artisan would have administered by the routes recited in claim 9, therefore, an artisan of skill would have be carry out extensive experimentation to administer DSG and determine whether DSG would be able to produce its immunosuppressant effect when administered by different routes or what doses would be required to produce the increase in tolerance.

Next the specification describes two examples. Example 1 teaches that in 50% animals (mice) that were treated with DSG only for 5 days after vector administration, 10% of the maximal expression of the transgene was observed on the 42nd day. The specification cite a PNAS paper for the recombinant adenovirus used in the experiment (see lines 35-39 of page 8 of the specification). It is noted that the cited paper teaches construction of adenovirus vectors that have deletions or insertions in the E1 or E3 regions, which indicates that different vectors of the paper would produce different levels of immune response. Therefore, it is unclear as to what was the contribution of DSG in the maintaining the lever of beta-galactosidase in the mice or whether the observed results were due to deletion of different genes of adenovirus. Example 2 describes the effect of DSG on alpha 1-antitrypsin

expression by adenoviral vector in a NMRI mouse. Administration of DSG i.p. for 5 days resulted in about 6 fold difference in the serum level of alpha 1-antitrypsin at almost all-different time intervals studied (see columns 4 and 5 in table 1). However, comparing the results of example 1 and 2, there was about 50% level of the maximum expression level (day 30) in the DSG treated group. These results indicate that there is an effect of the transgene used. It is noted that the specification discloses that alpha 1-antitrypsin used in example 2 is not antigenic. Therefore, one could assume that the higher protein levels in example 2 could be due to lack of antigenicity of the transgene product. In other words, the protection produced by DSG would depend on the protein encoded by the transgene. Tripathi et al observed that immune response directed against foreign transgene-encoded proteins are the major determinants of the stability of gene expression following intramuscular injection of recombinant adenoviral vector (see the abstract). The specification does not provide sufficient evidence as to whether the protection produced is all because of the protein product antigenicity or because of the adenoviral antigenicity and therefore an artisan has to carry out experimentation of trial and error to determine whether DSG would have provided protection when different transgene were used in the claimed method. Regarding adenoviral vector mediated gene therapy, Trapnell et al noted that the factors that affect the host immune response are: the dose of the vector; the route of administration; the level of replication (if replicating vector); the nature of the transgene contained in the recombinant vector; the genetic and physiological characteristics of the host; and the existence and level of pre-existing immune responses to previously administered adenovirus vectors (see page 12, last but one paragraph in Trapnell et al. WO96/12406, 5-2-1996). It is noted that DSG prevents humoral antibody response against adenoviral vector however, it is not known whether DSG also prevents other host immune response, inflammatory responses and even in case of humoral response, in the absence of any teachings from the specification as to what doses of adenovirus would be used, an artisan would

not know as to what doses of DSG to use so as to increase transgene expression. Regarding claims (7, 14, and 15) which recite methods that are directed to treatment of specific diseases such as diabetes or AIDS, or DNA vaccination, the specification does not provide any guidance as to how the methods of treatment of these disease would be carried out. Furthermore, since a subject would have been immnocompromized in AIDS or would have increased immune response in an autoimmune disease such as in diabetes, the specification does not provide any guidance as to what doses of the DSG would be used or what routes of administration would be use or which transgene would be used such that the effect of the transgene induced immune response is decreased by DSG treatment.

Next the specification is not enabling for the claimed method when transgenic cells are transplanted in a mammal or in a man because the state of the art of cell transplantation, except for autologous cell transplantation which would produce minimal immune response, is unpredictable. Hardy and Marvin (Transplantation proceedings 31:2949-2950, 1999) noted, "The problems of cell isolation, preservation, and avoidance of rejection have been defined but only partially solved" (see last sentence in the first paragraph, continued from page 2949 right column, on page 2950 left column). Additionally, there is a difference between the T cell response produced during allreactivity and xenoreactivity. For example, Gill et al noted that one of the characteristics of alloreactivity is an unusually high number of T cells whereas in the xenogeneic situation, the T cell dependent response tends to decrease in vitro as the phylogenetic disparity increases, but there are indirect pathways that are responsible for the reaction (see right column on page 362 continued into the left column on page 363). The specification does not provide guidance as to which of these pathways does DSG affect and whether DSG administration would provide any protection against allogeneic cells transplanted. It should be noted that with cell transplantation, immune response due to transplanted cells, the vector, and the therapeutic prtoeins, all the three would be responsible for the immune

response and the specification, except for the protection when adenoviral vector is administered to a mice, does not provide any guidance as to how an artisan would have practiced the claimed method when transplanting allogeneic or xenogeneic cells. Regarding xenotransplantation, these authors noted, "The holy grail of transplantation is xenotransplantation. The attraction of this method of transplantation is the pan-availability of organs from animal donors. However, the immunological barriers to successful xenotransplantation have been difficult to conquer. .....Under new breakthroughs in xenotransplantation and/or cloning occur, efforts at enhancing the currently available donor pool must be explored." This clearly indicates that xenotransplantation was not routine in the art and that immunosuppressant therapy could remedy the xentranplantation related immunological barriers, in addition to the immune response to the transgene encoded protein, such that the xenotransplanted cell would not be rejected. In addition to the issue of xenotransplantation, even when cells of same species (allogeneic cells) are used in transplantation, the immune response varies from cell type to cell type (see last paragraph in left column on page 21 in Cage, FH. Nature 392 (suppl):18-24,1998), for example, cells that express HLA on their surface induce rejection. Again in addition to the role of the cell in rejection, the transgene encoded protein will also add to the immune response. The specification fails to provide any guidance as to how an artisan of skill would have practiced the claimed method using allogeneic or xenogeneic cells expressing a transgene and therefore an artisan of skill would require extensive experimentation to practice the claimed method since the art of cell transplantation is unpredictable.

It is noted that claims 5-814, and 15 are directed to gene therapy. While the specification discloses that neither the production process of the transgenic cells nor the genetic material per se are of decisive importance for the invention, it is made of record that at the time of the invention the art of gene therapy was unpredictable. For example, Anderson (Anderson WF. Nature 392 (SUPP):25-30, 1998) noted that since the approval of first

clinical trial of gene therapy protocol in 1990, more than 300 protocols had been approved worldwide. He further added, "The conclusions from these trials are that gene therapy has the potential for treating a broad array of human diseases and that the procedure appears to carry a very low risk of adverse reactions; the efficiency of gene transfer and expression in human patients is, however, still disappointingly low. Except for anecdotal reports of individual patients being helped, there is still no conclusive evidence that a gene therapy protocol has been successful in the treatment of a human disease." Therefore, the claimed invention is not enabled for a method of gene therapy. It is emphasized that since the overall objective of a method of gene therapy would be to treat a disease by providing a candidate therapeutic protein to a disease cell, it is crucial that sufficient amount of the therapeutic protein is produced and maintained. And at the time of the invention, neither the prior art or the specification taught that such could be achieved and the specification does not provide any guidance as to how to address art recognized limitations of the gene therapy.

In summary, the state of the art of transgenic cell transplantation in a mammal or in man is unpredictable for several limitations as discussed above and therefore, in view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, one of ordinary skill in the art at the time of the invention would have required an undue amount of experimentation to make and use the claimed invention commensurate with the scope of the claimed invention. Accordingly, limiting the scope of the claimed invention to a method of increasing the tolerance of a mammal to transgenic cells, wherein the transgenic cells are produced in vivo after the administration of a vector carrying a transgene, by administering p15-deoxyspergualin to the mammal intravenously or intraperitoneally, before, during or after the administration of the vector, wherein said transgene encodes a protein, wherein a concomitant immunosuppressant therapy is discontinued, is proper.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1 and 4-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because it is unclear as to whether p15-deoxyspergualin is administered after discontinuing immunosppressant therapy. Claim 1 is also indefinite and the metes and bounds of the claimed invention is not clear because the specification does not define as to when or at what time after the administration of the transgenic cells and/or the immunosuppressant, the immnosuppressant therapy is discontinued.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1, 4, 9, 10, and 12 are rejected under 35 U.S.C. 102(a) as being anticipated by Smith et al (Gene Therapy 3:496-502, 1996; abstract only).

Smith et al teach use of transient immunosuppression with DSG in mice injected intravenously with adenoviral vector carrying the beta-galactosidase gene. Smith et al administered DSG intravenously to the mice at time of the exposure of the adenovirus (see the abstract) first time and observed that administration of DSG permitted an effective second

administration of a factor IX vector, without any immunosuppression afterwards.

Accordingly, the claimed invention is anticipated by Smith et al.

12. Claims 1, 4, 9, 10, and 12 are rejected under 35 U.S.C. 102(a) as being anticipated by Trapnell et al (WO 96/12406, 05-02-1996).

Trapnell et al teaches a method of administering a host concurrently with an adenoviral vector that expresses a therapeutic gene of interest and immunosuppressive agents, such as DSG (see the entire document). Example 3 discloses administration of DSG i.p. once daily beginning the day before administration and continuing for a total of eight days (see page 33, last paragraph). Figure 17 of Trapnell et al shows the human factor IX levels in mice that were administered adenoviral vector expressing factor IX alone or along with DSG or other immunosuppressants. Page 42 (last paragraph) discloses that five weeks after vector administration, no detectable levels of neutralizing antibodies were observed. Trapnell et al also discloses that DSG immunosuppression also allows readministration of the adenoviral vector (see the last paragraph on page 44 continued on page 45). Claim 1 of Trapnell et al recites a method of gene therapy treatment by administering to a host an adenoviral vector including at least one DNA sequence encoding a therapeutic protein and an immunosuppressive agent and discontinuing administration of said adenoviral vector and said immunosuppressive agent. Claims 10-11, and 14 recite that the immunosuppressive agent is DSG. Claims 19-21 recite that the immunosuppressive agent is administered prior to, at the same time or after the administration of the adenoviral vector. It is noted that while the claims of Trapnell recite readministration of the vector and DSG, DSG administration is only provide for certain period of time and then discontinued (see page 33, last paragraph).

Therefore, the claimed invention is anticipated by Trapnell et al.

13. No claim is allowed.

Applicants are advised to submit a clean version of each amended claim (without underlining and bracketing) according to § 1.121(c) and a copy of all the pending/under consideration claims. For instructions, Applicants are referred to http://www.uspto.gov/web/offices/dcom/olia/aipa/index.htm.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached on (703) 305-6608. The fax phone number for this Group is (703) 308-4242. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the Kay Pinkney whose telephone number is (703) 305-3553.

Ram R. Shukla, Ph.D.

RAM R. SHUKLA, PH.D
PATENT EXAMINER